REMARKS

The Applicant acknowledges, with thanks, receipt of the Office Action mailed February 12, 2003.

Claims 33-40, 42, 43, 47-50 and 55-58 are pending in the application. The action by the Examiner of this application, together with the cited references, have been given careful consideration. It is respectfully requested that the Examiner reconsider the claims in their present form, together with the following comments, and allow the application.

The Examiner rejected claims 33-40, 42-43, 49-50 and 55-58 under 35 U.S.C. §112, Second Paragraph as being indefinite for failing to distinctly claim the subject matter which applicant regards as the invention. The Examiner also rejected claims 47-48 under 35 U.S.C. § 112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventor had possession of the claimed invention. The Examiner rejected claims 33, 55 and 37-50 under 35 U.S.C. § 112, First Paragraph, as the specification is not enabling for an *in vitro* assay wherein the viral replication factor is EBNA-1 antigen. Further, the Examiner rejected claims 33-35 and 55 under 35 U.S.C. §102(b) as being anticipated by Gassmann et al. The Examiner rejected claims 33, 36, 56, and 57-58 under 35 U.S.C. §103(a) as being unpatentable over Gassmann in view of Cooper et al. and Carstens et al. Finally, claims 37-40, 42-43 and 47-50 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gassmann in view of Cooper and Carstens, and further in view of Lok, Williams et al., Moreau et al., and Nichols et al. Applicant respectfully traverses the rejections.

Claims 33-40, 42-43, 49-50 and 55-58 are in Condition for Allowance

Under 35 U.S.C. §112, Second Paragraph

Claims 33-40, 42-43, 49-50 and 55-58 were rejected under 35 U.S.C. §112, Second Paragraph. Applicant respectfully traverses.

Claim 33 and its dependent claims, and claim 58 were rejected as being incomplete for omitting essential steps. Specifically, the omitted step is the step of assaying the biological effect of the presence of a protein or polypeptide or other product of DNA expression in the recited mouse cell. Thus, claims 33 and 58 have been amended by insertion of a positive action step for assaying; part (e) which recites "and assaying the biological effect of expression of the protein or peptide or other product of cDNA expression". The Examiner's objections to these claims for omitting an essential step, are now moot.

It is the Examiner's position that the phrase in claim 35, "transfecting the mouse cell of step (b)" is unclear, in that it is unclear whether the step of transfection with a third vector is before or after the transfection with the second vector. Thus, claim 35 was amended to refer to step (c) of Claim 33, rather than step (b). This amendment is in accordance with the Examiner's suggestion.

It is also the Examiner's position that there is insufficient antecedent basis for the limitation of claim 36, "each of the cDNAs according to the method of claim 33", as there is no recitation of any cDNAs in claim 33. Thus, claim 33 was amended to recite cDNAs rather than just DNAs, thereby providing antecedent basis for this term in Claim 36. The Examiner's objections to lack of antecedent basis is now moot.

The Examiner states that in claim 37 and its dependent claims, it is unclear what is encompassed by the phrase "expressing.....in a mouse cell" in step (a). The Examiner's suggested wording, "(a) expressing in a mouse cell selected from the group consisting of an ES cell, an EC cell, an EG cell, and differentiated progeny thereof, a composite DNA...", has been adopted for claim 37.

Therefore claims 33-40, 42-43, 49-50 and 55-58 are in condition for allowance under 35 U.S.C. §112, Second Paragraph.

Claims 47-48 are in Condition for Allowance

Under 35 U.S.C. §112, First Paragraph

Claims 47-48 were rejected under 35 U.S.C. §112, First Paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention. Applicant respectfully traverses.

Specifically, claims 47-48 recite "otherwise obtaining a transgenic mouse cell, selected from the group consisting of an ES cell, an EC cell and an EG cell, that expresses the replication factor". The Examiner states that there is no support for Applicant's contemplation of using the selected transgenic mouse cell expressing the replication factor in the methods as claimed. Thus, claims 47-48 have been amended, such that step (a) (ii) that recites obtaining a cell from a transgenic mouse has been deleted. These claims now only refer to episomal vector embodiments of the invention. Thus, the Examiner's objections are now moot.

Claims 33, 55, and 37-50 are in Condition for Allowance

Under 35 U.S.C. §112, First Paragraph

Claims 33, 55, and 37-50 were rejected under 35 U.S.C. §112, First Paragraph, due to the fact that the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with these claims. Applicant respectfully traverses.

It is the Examiner's position that the specification, while being enabling for the *in vitro* assay of claim 33, wherein the viral replication factor is selected from polyoma large T antigen, papilloma virus replication factors, and SV40 large T antigen; and the *in vitro* method of claim 37, wherein the mouse cell is selected from an ES cell, an EC cell and an EG cell; but does not reasonably provide enablement for the *in vitro* assay wherein the viral replication factor is EBNA-1 antigen. Thus, the EBNA-1 antigen has been deleted from Claim 55.

Therefore claims 33, 55, and 37-50 no longer relate to EBV based episomal vectors. Consequently, these objections are now moot.

With respect to claims 37-50, the Examiner states that it is unclear how one can determine if a cell differentiates or not in the *in vitro* assay as claimed, when differentiated progeny of a mouse ES cell, a mouse EG cell or a mouse EC cell is a starting material. Therefore, claim 37 part (b) has been expanded to explain how differentiation of the cell progeny is monitored. Differentiation of cells is a process that is commonly monitored and routine in the art. Already differentiated cells can differentiate further, and this can be monitored using expression of phenotypic markers or cell morphology as a guide. Thus, the Examiner's objections with respect to claims 37-50 are now moot.

Therefore, all claims are in condition for allowance under 35 U.S.C. §112.

Claims 33-35 and 55 are in Condition for Allowance

Under 35 U.S.C. §102(b)

The Examiner rejected claims 33-35 and 55 under 35 U.S.C. §102(b) as being anticipated by Gassmann et al. The Examiner states that Gassmann discloses as an exemplification the preparation of mouse ES clone 1.19 cells that contain episomal pMGD20neo DNA and express the polyoma large T antigen.

Gassmann *et al.* (1995) demonstrates establishment of a two episomal vector system in mouse embryonic stem cells. In Gassmann, a mouse ES cell contains a first vector which expresses the Polyoma large T antigen replication factor and supports the replication of a second vector, which although not expressing the replication factor itself, does comprise an origin of replication targeted by the replication factor from the first vector.

The second Gassmann vector, denoted PGK*hph*ΔLT20, comprises the Polyoma *Ori* sequence, the Large T gene with a 1249 bp deletion in its coding sequence and a hygromycin B resistance selectable marker gene (p.1295, left hand column). Expression of the selectable marker was under the control of the phosphoglycerate kinase (PGK) promoter.

Gassmann *et al.* teaches that the second vector comprises a PGK cassette directing the expression of a hygromycin resistance selectable marker but does not disclose the presence of any further expression cassettes for expression of other - non selectable marker - DNAs such as cDNAs.

A key difference between the vector described in Gassmann *et al.* and that described in the Applicants' invention is that the Applicants have deleted the majority of the polyoma large-T sequence from the second episomal vector (Description page 20, paragraph 2). This increases the capacity for DNA inserts to be cloned into the vector by reducing the size of the vector backbone and surprisingly, it has been found that stable high level expression from the second vector can be obtained with the large T sequence substantially removed (see page 23, second paragraph).

In addition, Applicants' vector contains a second DNA expression cassette. The second expression cassette provides for the expression of an exogenous inserted DNA, such as a cDNA.

Following the teaching of Gassmann, a person of skill in the art would have believed it was necessary to maintain some component of the polyoma large-T sequence in the second vector to ensure replication of the second episomal vector in the mouse ES cells. A person of skill in the art would have retained the majority of the gene encoding the polyoma large-T antigen, so as not to adversely affect replication of the second episomal vector in the mouse ES cells.

The skilled person would have expected the present two vector (or more) system to fail because essential portions of the large-T sequence are inevitably omitted from the second vector.

Hence, the present invention is distinguished from Gassmann *et al.* in that the second vector comprises both a selectable marker and a cDNA expression cassette that is not a selectable marker, whereas Gassmann *et al.* describes only that the second vector contains a selectable marker.

The Examiner acknowledges on page 7 (lines 9-10 of the Office Action) that Gassmann does not describe a method for screening cDNAs. Claim 33 as amended now recites an assay for a biological effect of a product of cDNA expression, wherein the second vector contains a cDNA and a DNA coding for a selectable marker.

Gassmann also does not relate to screening libraries of cDNAs, wherein claims 33 and 47 have been amended by insertion of the additional step previously recited in Claims 34 and 48 respectively, to relate to screening libraries. As such, Gassmann does not teach dividing the cells transfected with the first episomal vector into batches which are then transfected with different second vectors.

Hence, the claims as amended are novel over Gassmann *et al.*

Claims 33, 36, 56 and 57-58 are in Condition for Allowance

Under 35 U.S.C. §103(a)

The Examiner rejected claims 33, 36, 56 and 57-58 under 35 U.S.C. §103(a) as being unpatentable over Gassmann et al. in view of Cooper et al. and Carstens et al. The Examiner states that it would be obvious for one of ordinary skill in the art to adapt the episomal plasmid vector system taught by Gassmann in light of the teachings of Cooper and Carstens to divide mouse ES cells harbouring a first episomal vector expressing polyoma large T antigen into two distinct cell populations for subsequent transfections with two distinct episomal vectors coding for different gene products to assay for their biological effects.

As explained above, Gassmann does not describe expression of a cDNA from the second vector, or how to go about achieving this. Gassmann also does not teach how to screen cDNA libraries using his two vector system, this point has been acknowledged by the Examiner (lines 9-10, page 7).

The Examiner has combined the teaching of Gassmann with that of Carstens and Cooper. The Examiner suggests that the skilled person could have read these citations together in order to arrive at the methods of the present invention.

Applicant's respectfully disagree with the Examiner, as the skilled person could not have read Gassmann in conjunction with Carstens and Cooper since they represent conflicting documents spread over different and divergent fields of art. In order to demonstrate how different these documents are, provided is a side-by-side comparison of the salient features of these documents below.

Gassmann	two vector system	in mouse ES cells	uses polyoma large T replication factor
Carstens	one vector system	in human fibroblasts	uses EBNA- 1 (unsuitable for rodent cells) replication factor
Cooper	one vector system	in human carcinoma	uses BKV replication factor

It is evident that Carstens is performed in non-ES cells and utilizes a replication factor system based on epstein-barr virus that cannot be performed in rodent cells. Carstens clearly states that the EBNA-1 system is unsuitable for use in rodent cells on page 196 (column 2, first sentence of results section). Carstens *et al.* teaches the use of a one vector system in human fibroblasts utilizing a replication factor system that could not be used in mouse cells as currently claimed in the present invention.

The additional citation of Cooper describes a one vector system in human bladder carcinoma cells (column 5, line 22). Therefore, Cooper does not add anything further and the skilled person seeking to express cDNA sequences in mouse ES cells would not have used a system optimized for use in human bladder carcinoma cells.

As such, Gassmann, Carstens and Cooper could not be reasonably combined in order to render the present claims as amended obvious.

Claims 37-40, 42-43 and 47-50 are in Condition for Allowance

Under 35 U.S.C. §103(a)

The Examiner rejected claims 37-40, 42-43 and 47-50 under 35 U.S.C. §103(a) as being unpatentable over Gassmann et al. in view of Cooper et al. and Carstens et al., and further in view of Lok, Williams et al., Moreau et al., and Nichols et al. The Examiner states that it would be obvious for one of ordinary skill in the art to modify the episomal vector system taught by Gassmann, in which a DNA coding for a leaderless leukemia inhibitory factor (LIF or IL-6) or a leaderless IL-6 receptor is used to trap NH2-terminal signal encoded sequences, and select for cells containing DNA coding for signal sequences under suitable conditions based on the differentiation state of mouse ES cells in culture, in light of the combined teachings of Cooper, Carstens, Lok, Williams, Moreau, and Nichols.

The above comments with regards to the lack of compatibility between Gassmann, Carstens, and Cooper removes the alleged link between the Gassmann two vector system and art utilizing methods designed for human somatic cells. In general, it is not reasonable to assume that the skilled person could have taken and applied techniques described for use in human somatic cell lines and expected these to function in an identical and analogous matter in mouse embryonic stem cells, embryonal carcinoma cells or embryonic gonadal cells. At the very least, the skilled person would be forced to undertake undue levels of experimentation in order to generate a system that was functional in ES cells.

In order to object on the grounds of obviousness there must be clear motivation in the art that would have prompted the skilled person to arrive at the present invention with little more than minor routine modifications to existing protocols. This is manifestly not the case in the present application, the skilled person would have had to conduct extensive trials in order to determine whether the human cell line based assays could be modified for use in the technically difficult ES cell system.

Thus, for the reasons set forth, claims 33-40, 42, 43, 47-50 and 55-58 are in condition for allowance.

In view of the foregoing, it is respectfully submitted that the present application is now in proper condition for allowance. If the Examiner believes there are any further matters

which need to be discussed in order to expedite the prosecution of the present application, the Examiner is invited to contact the undersigned.

If there are any fees necessitated by the foregoing communication, please charge such fees to our Deposit Account No. 50-0902, referencing our Docket No. (78870/32777).

Respectfully submitted,

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I hereby certify that this correspondence (along with any paper referenced as being attached or enclosed) is being deposited on the below date with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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